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REVIEW ARTICLE

Oxadiazole and their Synthetic Analogues: An Updated Review

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ABSTRACT

Oxadiazole and its tested derivatives with diverse pharmacological activities come under an important class of compounds in new drug development. The novel oxadiazole derivatives synthesized and investigated for their chemical and biological behavior has showed more importance in the recent era. In the previous studies, it was found that synthetic modification of oxadiazole ring has higher efficacy with improved potency and lesser toxicity. The present review provides an overview on the work done so far on oxadiazole and its biological activities (2008-2018).

Keywords: Antibacterial, anticancer, anti-hepatitis, anti-inflammatory, antimicrobial, oxadiazole.

INTRODUCTION

Heterocyclic moieties have been explored with the aim of developing pharmaceutically active molecules in the pharmaceutical industry. Out of them, the derivatives of oxadiazoles have shown significant role in the medicinal chemistry. Oxadiazole is a five-membered heterocyclic moiety having two carbons, two nitrogens, one oxygen, and two double bonds having general formula $C_2H_2ON_2$.[1,2] In general, 1,3,4-oxadiazoles are prepared by the reactions of acid hydrazides or hydrazine with carboxylic acids/acid chlorides and direct ring closure of diacylhydrazines employing different kinds of dehydrating agents such as phosphorous oxychloride,[3] thionyl chloride,[4] phosphorous pentaoxide,[5] triflic anhydride,[6] polyphosphoric acid,[7] and direct reaction of acid with (N-isocyanimino-)-triphenylphosphine.[8-11] Differently substituted oxadiazole moieties have also been found to possess other attention-grabbing activities such as analgesic,[12,13] antimicrobial,[14] antitubercular,[15] anticonvulsant,[16] and anti-hepatitis B viral activities.[17]

OXADIAZOLE DERIVATIVES AND CHEMICAL ANALOGS

Dhara *et al*. synthesized new oxadiazole derivatives [Figure 1] and almost all the newly synthesized compounds especially some of them displayed remarkable growth inhibition against three bacterial strains: *Mycobacterium smegmatis, Staphylococcus aureus,* and *Escherichia coli* and fungi *Candida albicans*. Later on, the antimicrobial activity was confirmed by minimum inhibitory concentration (MIC) assay against the same microorganisms. Among them, the compound 5 g displayed promising activity with a MIC value of 0.025 mM for two bacteria and fungi, whereas the MIC of this compound for *E. coli* was 0.1 mM. Other active compounds also exhibited good MIC ranging between 0.313 and 5.0 mM against the selected microorganisms. Docking simulations were generated to discover the potential binding approaches of ligand 5g at the D-alanine: d-alanine ligase protein of *E. coli* and *S. aureus*.[18]

Kaya *et al.* designed and synthesized a series [Figure 2] of hydrazide and oxadiazole derivatives with the aim of new cytotoxic and antimicrobial agents with improved antitumor activity. Among the compounds evaluated, compound 7c bearing 1,3,4-oxadiazole ring and 6-methoxy benzothiazole moiety exhibited the highest inhibitory activity against A549 and MCF-7 tumor cell lines in contrary to NIH/3T3 cell line, as desired.[19]

Mihailovic *et al.* reported novel eight 1,3,4-oxadiazole derivatives [Figure 3]containing phenolic acid moieties and eight of their diacylhydrazine precursors and characterized with the help of spectroscopic methods and further they are examined by scavenging of stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. The phenolic 1,3,4-oxadiazoles

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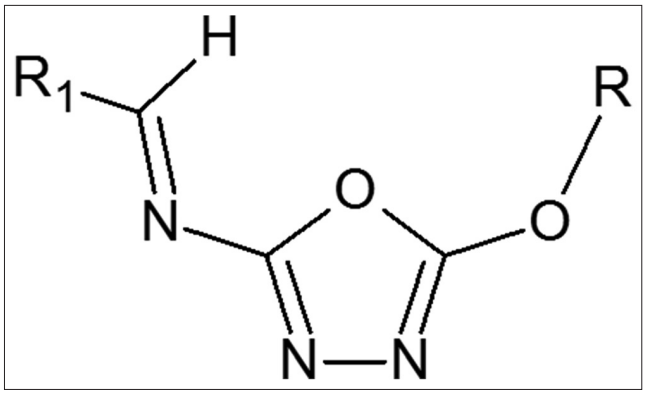

Figure 1: 2-[2-substituted ethenyl]-5-(substituted methoxy)-1,3,4-oxadiazole derivatives

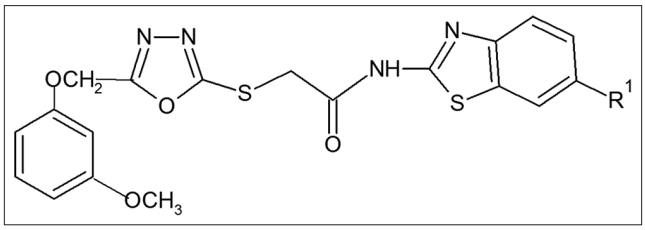

Figure 2: N-(6-substitutedbenzothiazol-2-yl)-2-[(5-[(3-methoxyphenoxy)methyl]-1,3,4- oxadiazol-2-yl)thio] acetamide derivatives

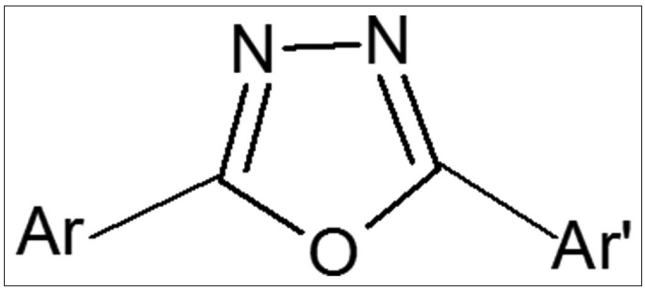

Figure 3: 2,5-disubstituted-1,3,4-oxadiazole derivatives

derivatives have showed superior DPPH scavenging activity as they are highly potent as compared with their corresponding diacylhydrazine precursors which result due to the contribution of both aromatic rings and a 1,3,4-oxadiazole as they are in resonance stabilization of the formed phenoxyl radical.[20]

Doronells *et al*. synthesized a series of new 2,5-disubstituted 1,3,4-oxadiazoles under conventional thermal heating and microwave irradiation conditions through the reaction of acyl hydrazides with *N* protected *α*-amino acid in the presence of a small amount of $POCl_3$ [Figure 4].[21]

Bala *et al.* reported 1,3,4-oxadiazole substituted 24 derivatives [Figures 5 and 6]and carried out their antibacterial activity against selected microbial strains in comparison with Penicillin and Cefixime. They also studied their physicochemical and structural properties by QSAR analysis using computer-assisted multiple regression analysis, and four sound predictive models were generated

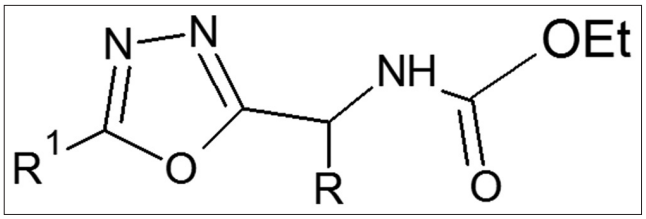

Figure 4: 2,5-disubstituted-1,3,4-oxadiazole derivatives

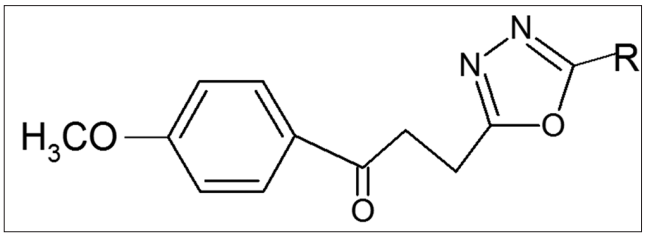

Figure 5: 1-(4-methoxy-phenyl)-3-[5-(substitutedphenyl)-1,3,4-oxadiazol-2-yl]propan-1-one

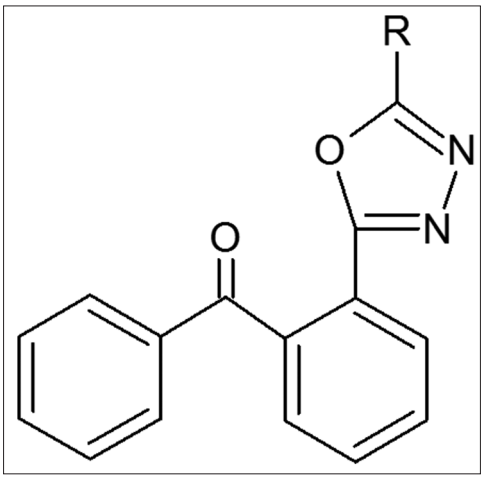

Figure 6: [2-(5-substituted-phenyl-[1,3,4]oxadiazol-2-yl)-phenyl]phenyl-methanone

with good R2, R2adj, and Fischer statistic.[22]

Thasneem *et al.* prepared chalcone linked 1,3,4-oxadiazole derivatives and the newly synthesized compounds were characterized by infrared (IR), 1H nuclear magnetic resonance (NMR), MASs SPECTRAL analysis, and evaluated for anticancer activity on human breast cancer cell line MCF 7. The derivatives showed significant activity on MCF 7 cell line [Figure 7].[23]

Rashidi and Berad developed some novel derivatives of N-(4-chlorophenyl) amino-5-aryl-1,3,4-oxadiazole [Figure 8] by condensing various acid hydrazides with 4-(chlorophenyl) isocyanodichloride. Structural confirmation of all the newly synthesized compounds was done on the basis of IR, 1H NMR, and mass spectral data.[24]

Chen *et al.,* in there study, synthesized and evaluated a series of 2-substituted-5-thiopropylpiperazine(Piperidine)-1,3,4-Oxadiazoles derivatives [Figure 9]. Further, their binding affinity to

different receptors has been checked, and it was found that compound 22 showed an atypical antipsychotic activity devoid of liability for extrapyramidal symptoms and it can be used to develop a new class of drug for the treatment of schizophrenia.[25]

Malhotra *et al.* synthesized new oxadiazole derivatives [Figure 10] of isonicotinohydrazide. In this structural modifications of the front line, antitubercular drug isoniazid provides lipophilic adaptations of the drug in which the hydrazide moiety of isoniazid is replaced by 1,3,4-oxadiazole heterocycles to eliminate *in vivo* acetylation by arylamine N-acetyltransferase, which results in the formation of the inactive acetylated drug. The new derivatives were evaluated for their antimicrobial activity by broth dilution method against two Gram-positive bacterial strains (*Bacillus subtilis* and *S. aureus*), two Gram-negative bacterial strains (*Pseudomonas aeruginosa* and *E. coli*), and two fungal strains (*C. albicans* and *A. niger*).[26]

Ali *et al.* investigated and synthesized disubstituted 1,3,4-oxadiazole derivatives [Figure 11] with the help of intramolecular aza-Wittig reaction of the iminophosphorane intermediates under neutral conditions and resulting in marvelous yields. This new artificial approach mentioned here has potential in the synthesis of various 2,5-disubstituted 1,3,4-oxadiazoles, having significant importance as potential biologically active compounds or pharmaceuticals.[27]

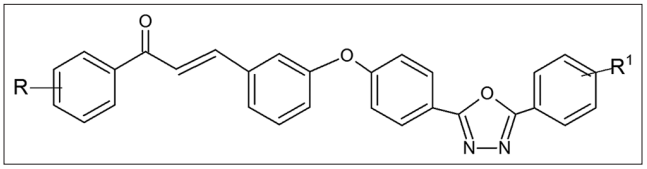

Figure 7: Chalcone linked 1, 3, 4 – oxadiazole derivatives

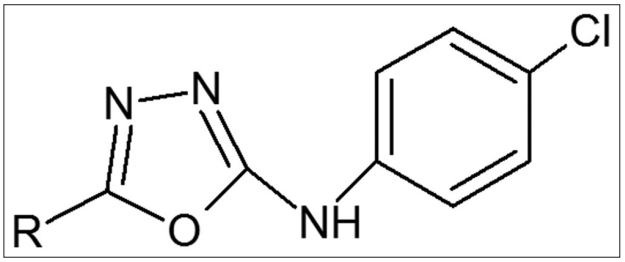

Figure 8: N-(4-chlorophenyl) amino-5-aryl-1,3,4-oxadiazole

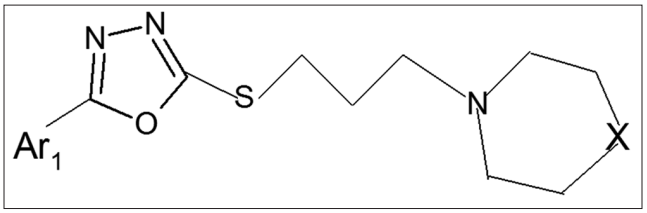

Figure 9: 2-Substituted-5Thiopropylpiperazine (Piperidine)-1,3,4-Oxadiazoles Derivatives

Dabholkar and Bhusari synthesized 2-substituted-1,3,4-Oxadiazole derivatives [Figures 12-14], and structural elucidation is done through spectral analysis. Further, the compounds were screened for their antimicrobial activity against Gram-negative as well as Gram-positive bacteria, which have shown convincing activity.[28]

Deshmukh *et al.* designed a series of 2-aryl-7alkyl or aryl-(1,3,4)-oxadiazole(3,2-a) (1,3,5) triazin-5-one, and 2-aryl-7alkyl [Figure 15]or aryl–(1,3,4-)oxadiazole(3,2-a) (1,3,5)triazine-5-thione [Figure 16], and synthesized them. The structures of new compounds have been confirmed by spectral and analytical data. The newly synthesized compounds have been evaluated for their antibacterial activity.[29]

Kaplancikli, in his study, synthesized 5-[(pyrimidin-2-ylthio)methyl)-1,3,4-oxadiazole-2(3H)-thione [Figure 17] through ring closure reaction of 2-(pyrimidin-2-ylthio)acetohydrazide with the help of carbon disulphide. *In vitro* examinations of the newly synthesized compounds were done against *C. albicans, Candida glabrata, Candida*

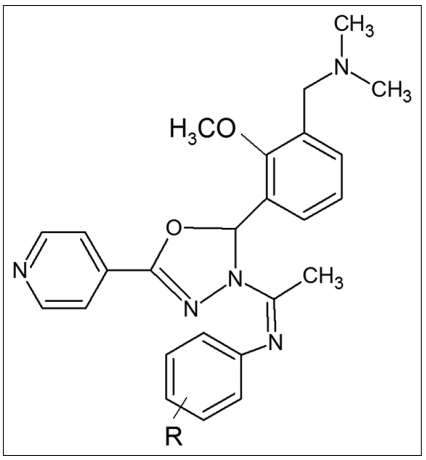

Figure 10: (Z)-N-(1-(2-(3-((dimethylamino)methyl)-2-methoxyphenyl)-5-(pyridin-4-yl)- -1,3,4-oxadiazol-3(2H)-yl)ethylidene)benzenamine derivative

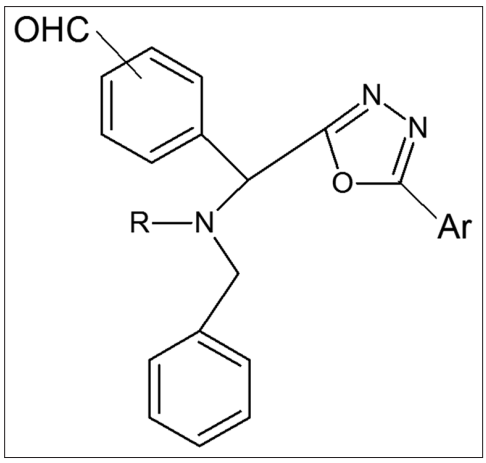

Figure 11: Sterically congested 1,3,4-oxadiazole derivatives

tropicalis, Candida krusei, Candida Parapsilosis, and comparision were done with ketoconazole.[30] Sahoo *et al.,* in his study, prepared some of the novel 5- phenyl- 1, 3, 4- oxadiazole- 2- thiol derivatives [Figure 18] by the ring closure reactions of benzohydrazides with carbon disulphide in the existence of ethanolic KOH followed by an exchange with secondary amines at 2nd position. Spectral analysis of the freshly synthesized compounds was done with the help of IR, NMR, and liquid chromatography-mass spectrometry. Most of them showed significant anti-inflammatory and antibacterial activity.[31]

Mayekar developed a series of novel 1,3,4-oxadiazole derivatives [Figures 19 and 20] having 6-bromonaphthalene moiety. Analysis and characterization of the newly synthesized compounds were done by analytical and spectral data. Antimicrobial

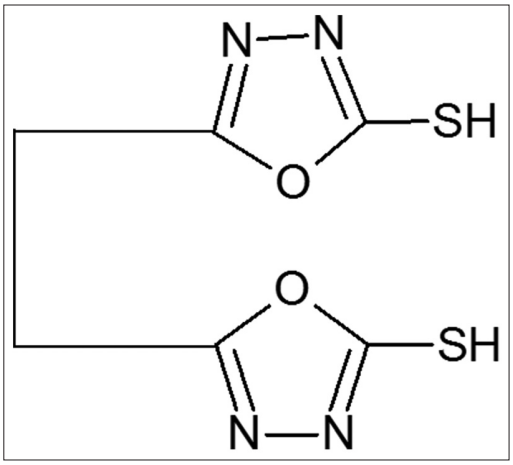

Figure 12: 1,2[di-(2-Mercapto-1,3,4-oxadiazole-5yl)] ethane

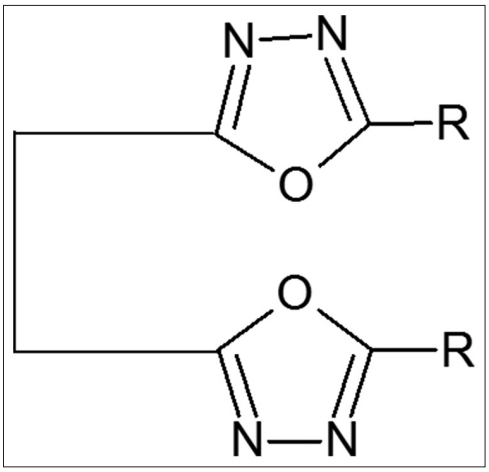

Figure 13: 1,2[di-(2-Phenyl-1,3,4oxadiazole-5yl)] ethane

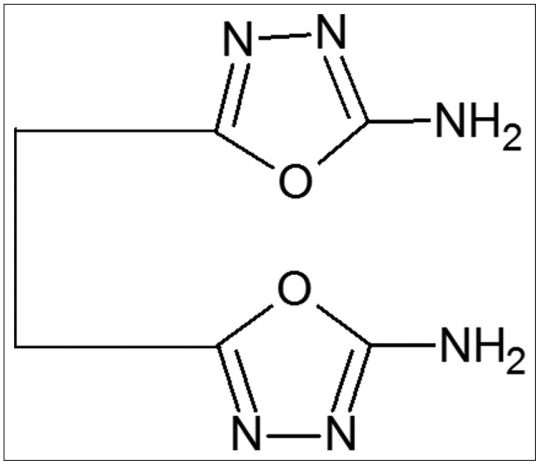

Figure 14: 1,2[di-(2-Amino-1,3,4-oxadiazole-5 yl)] ethane

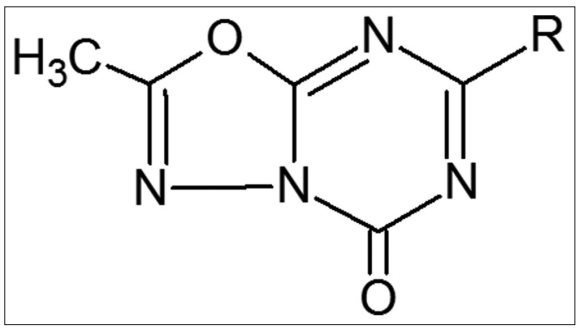

Figure 15: 2-aryl-7alkyl or aryl-[1,3,4]-oxadiazolo[3,2-a] [1,3,5]triazin-5-one and 2-aryl-7alkyl

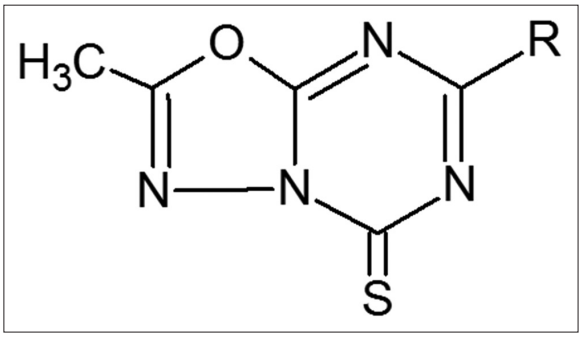

Figure 16: 2-aryl-7alkyl or aryl–[1,3,4]oxadiazolo[3,2-a] [1,3,5]triazine-5-thione

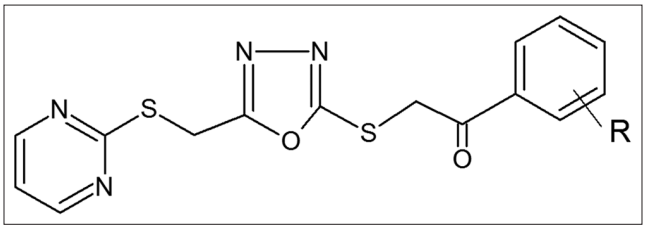

Figure 17: 2-[5-[(Pyrimidin-2-ylthio)methyl]-1,3,4-oxadiazol-2-ylthio]acetophenone derivatives

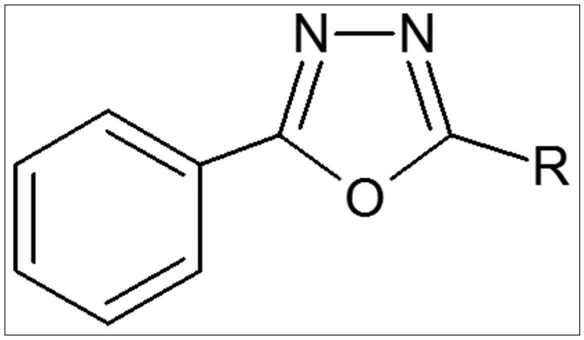

Figure 18: 5- phenyl- 1, 3, 4- oxadiazole- 2- thiol derivative

activities of these compounds were carried out, and some of them have exhibited good activity.[32]

Husain and Ajmal synthesized, a series of 2-(3-(4-bromophenyl)propan-3-one)-5-(substituted phenyl)-1,3,4-oxadiazoles [Figure 21] from 3-(4-bromobenzoyl)propionic acid with the aim of developing a new compound with better anti-inflammatory and analgesic activity but with minimal side effects.[33]

Islam *et al.* reported a series of 5-{3'-oxo-6'-(substituted aryl)-2',3',4',5'-tetrahydropyridazin-2'-ylmethyl}-2-substituted 1,3,4-oxadiazole [Figures 22 and 23]. All the final compounds were structurally elucidated on the basis of IR, 1H-NMR, Mass Spectral data and elemental analysis and screened for antibacterial, antifungal, and antitubercular activity.[34]

DISCUSSION

Heterocyclic compounds comprising oxadiazole have been extensively explored for their role in the pharmaceutical industry. They have been found to be of significant use for their medicinal properties such as analgesic, anti-inflammatory, antimicrobial, anticancer, antitubercular, anticonvulsant, and anti-hepatitis B activity. This review emphasized the synthesis of various oxadiazole derivatives by numerous researchers and study of their physiochemical and structural properties by QSAR analysis, IR, NMR, mass spectral analysis, etc.

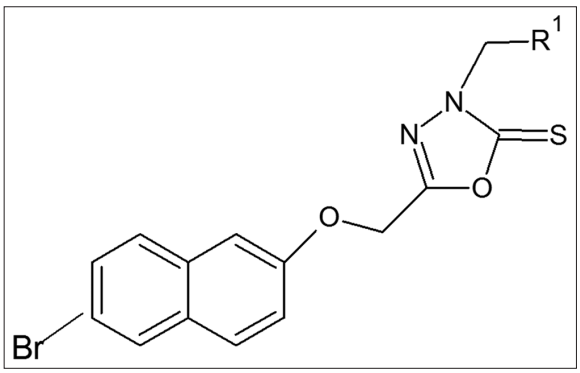

Figure 19: 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5-[(alkyl)thio]-1,3,4-oxadiazole

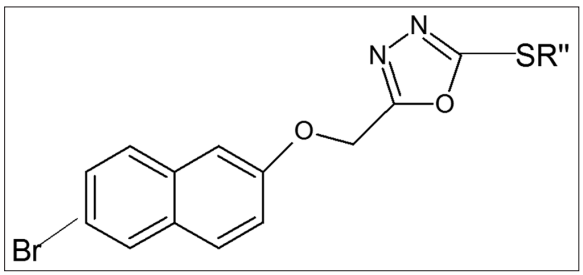

Figure 20: 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5-[(aryl) thio]-1,3,4-oxadiazole

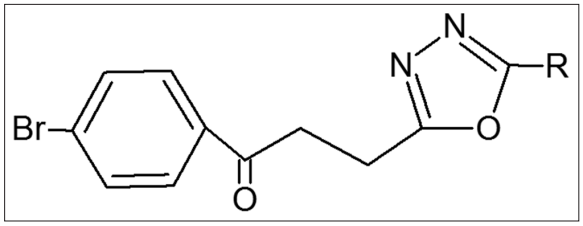

Figure 21: 2-[3-(4-bromophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole

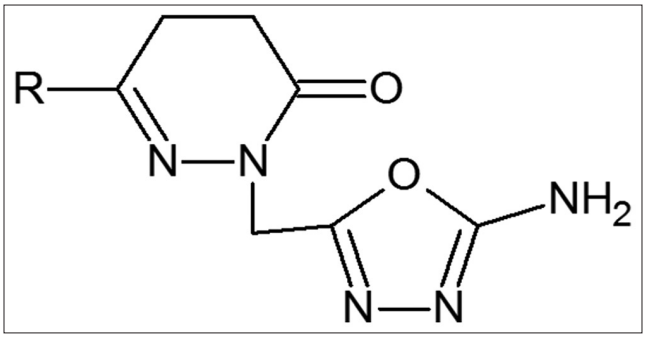

Figure 22: 5-{3í-oxo-6í-(substituted aryl)-2í,3í,4í,5í-tetrahydropyridazin-2í-ylmethyl}-2-amino-1,3,4-oxadiazole

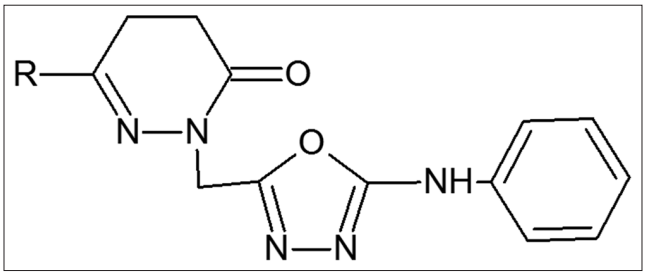

Figure 23: 5-{3í-oxo-6í-(substituted aryl)-2í,3í,4í,5í-tetrahydropyridazin-2í-ylmethyl}-2-phenylamino-1,3,4-oxadiazole

CONCLUSION

Oxadiazole and their chemical analogs have proved to be of significant value in the medical field by providing a promising role in the treatment of various diseases through their antimicrobial, antitubercular, and anticonvulsant properties, etc. Additional studies are required to determine the possible use of heterocyclic compounds in other fields.

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